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Substance P Potentiates the Algogenic Effects of Intraarterial Infusion of Adenosine

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Objectives. **This study investigated whether substance P potentiates the muscular and cardiac pain caused by the intraarterial infusion of adenosine, an autocoid known to induce muscular and cardiac ischemic-like pain in humans.**

Background. **Substance P is involved in the generation of neurogenic inflammation and causes cutaneous hyperalgesia. Because substance P is present in perivascular nerves it might also cause muscular and cardiac hyperalgesia. To test this hypothesis its effects on adenosine-induced muscular and cardiac pain were investigated in humans.**

Methods. **A randomized, crossover study of the algogenic effects of the intrailiac infusion of increasing scalar doses (from 125 to 2,000 μg/min) of adenosine or substance P (11.2 pmol/min) for 3 min, followed by the simultaneous infusion of substance P plus the same doses of adenosine, was carried out in nine patients with no evidence of peripheral vascular disease. A similar protocol was carried out by infusing increasing scalar doses of adenosine (from 50 to 800 μg/min) or substance P (11.2 pmol/min) for 3 min, followed by the simultaneous infusion of substance P plus the same doses of adenosine, into the left coronary artery of eight patients with angina. Pain severity, assessed by a visual analog scale, is presented as median. The remaining data are presented as mean value ± 1 SD.**

Results. **All patients experienced pain during both adenosine and substance P plus adenosine infusion; no patient experienced pain during the infusion of substance P alone. During intrailiac infusion, all patients experienced pain in the right leg that occurred earlier (207 ± 152 vs. 321 ± 154 s, $p < 0.05$) and was greater (47 vs. 30 mm, $p < 0.05$) during the simultaneous infusion of substance P plus adenosine than during the infusion of adenosine. Similarly, during intracoronary infusion, all patients experienced chest pain that occurred earlier (409 ± 242 vs. 596 ± 210 s, $p < 0.05$) and was greater (51 vs. 33 mm, $p < 0.05$) during the simultaneous infusion of substance P plus adenosine than during infusion of adenosine. No patient exhibited electrocardiographic signs of ischemia.**

Conclusions. **Substance P does not cause muscular or cardiac pain, but it provokes muscular and cardiac hyperalgesia.**

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Substance P is an 11-amino acid neuropeptide widely distributed in the central and peripheral nervous system (1). Substance P-like immunoreactive nerve fibers have been found in the atrium, in the conduction tissue and in the perivascular sensory nerves of many mammalian species, including humans (2,3). Since its discovery, substance P has received considerable attention with regard to the generation and transmission of nociceptive signals (4). Previous experimental and clinical studies have emphasized the potential role of substance P released from peripheral cutaneous nerve terminals in the generation of hyperalgesia, that is, a lowering of the pain threshold localized in an area of tissue damage (5,6). The intraarterial infusion of substance P does not appear to cause pain (7–11); however, it may cause hyperalgesia. This study investigated whether substance P potentiates the known algogenic effects caused by the intraarterial infusion of adenosine (12–15).

Methods

The study protocols were approved by the Institutional Ethics Committee in March 1992, and all patients gave written informed consent.

Adenosine and substance P preparation. Adenosine (2.7 mg/ml in ampules of 2 ml) (Sigma Tau Pharmaceutics)

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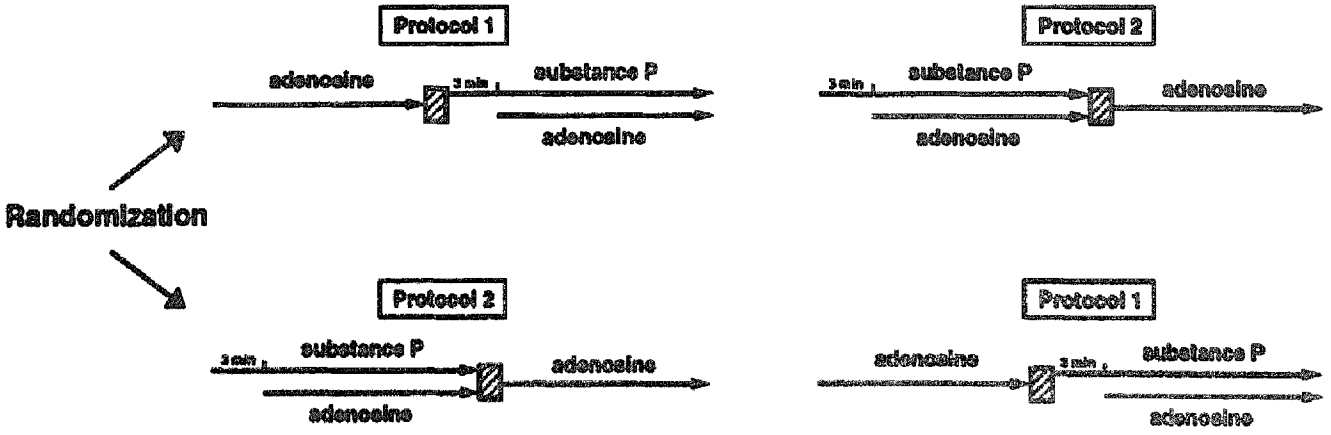


Figure 1. Diagrammatic representation of the infusion protocols for both intrailiac and intracoronary studies. **Protocol 1:** Adenosine was infused at increasing doses for periods of 2 (during intrailiac study) or 3 (during intracoronary study) min each. At the onset of pain, adenosine infusion was continued to complete the infusion period of that particular dose of adenosine. Infusion of adenosine was then stopped. Ten minutes after the disappearance of adenosine-induced pain, substance P alone was infused for 3 min, followed by the simultaneous infusion of increasing doses of adenosine. At onset of pain, adenosine plus substance P infusion was continued to complete the infusion period of that particular dose of adenosine. Infusion of adenosine plus substance P was then stopped. **Protocol 2:** Substance P alone was infused for 3 min followed by simultaneous infusion of increasing doses of adenosine. At onset of pain, adenosine plus substance P infusion was continued to complete the infusion period of that particular dose of adenosine. Infusion of adenosine plus substance P was then stopped. Ten minutes after the disappearance of pain, adenosine alone was infused at increasing doses for periods of 2 (during intrailiac study) or 3 (during intracoronary study) min each. At onset of pain, adenosine infusion was continued to complete the infusion period of that particular dose of adenosine. The infusion of adenosine was then stopped.

was stored at −60°C and was dissolved in normal saline solution to the final concentrations on the day of the study. Substance P (Cambridge Research Biochemicals) was dissolved in 10% acetic acid to a concentration of 1 mmol/liter, diluted further with normal saline solution to a stock solution of 2×10^{-4} mol/liter, and stored at −60°C. All further dilutions were prepared on the day of the study using normal saline solution. A matched stock solution of the acetic acid without substance P was also prepared and stored at −60°C. Further dilutions corresponding to that made for the preparation of substance P (11.2 pmol) were made with normal saline solution on the day of the study for the control infusion. Substance P solution and the vehicle were not additionally buffered.

Intrailiac study. A total of 18 consecutive male patients (mean [±SD] age 54 ± 9 years, range 37 to 70) with no evidence of peripheral vascular disease (ankle/brachial index >1 assessed by vascular Doppler) participated in this study. At the end of routine cardiac catheterization, nine patients underwent a randomized crossover study of the algogenic effects of the infusion of adenosine or the simultaneous infusion of substance P plus adenosine into the right external iliac artery by means of a 5F catheter (Fig. 1). In all patients the 5F catheter was inserted through a 7F femoral sheath. Adenosine was infused at increasing doses of 125, 250, 500, 1,000 and 2,000 μg/min for periods of 2 min each. Substance P alone (11.2 pmol/min) was infused at the rate of 2 ml/min for 3 min, followed by the simultaneous infusion of substance P (11.2 pmol/min) plus the same doses of adenosine. At the onset of pain the infusion of adenosine or substance P plus adenosine was continued to complete the infusion period of that particular dose of adenosine and was then stopped. The time to onset of pain (in seconds from the beginning of the infusion) and maximal pain severity, assessed by using a visual analog scale (16), were recorded. Five patients received adenosine; four patients received substance P plus adenosine as first infusion. Arterial blood pressure, obtained by way of the side port of the femoral sheath, and the standard 12 electrocardiographic (ECG) leads were recorded continuously throughout the study.

Nine other male patients (mean age 51 years, range 41 to 63) served as a control group. They received the intrailiac infusion of adenosine and the simultaneous infusion of substance P vehicle plus adenosine using the same protocol specified previously. Five patients received adenosine, whereas four received substance P vehicle plus adenosine as first infusion.

Intracoronary study. Eight patients (seven men, one woman; mean age 58 years, range 44 to 65) with stable angina pectoris and significant left coronary atherosclerosis participated in this study. No patient had a previous myocardial infarction. All patients had exercise tests positive for myocardial ischemia with horizontal or downsloping ST segment depression ≥2.0 mm and anginal pain. All patients had at least one significant coronary artery stenosis (internal diameter reduction >70% by visual assessment). In particular, three patients had significant stenosis in the left anterior descending coronary, three patients had stenosis in the proximal circumflex coronary artery, and two patients had significant lesions in both arteries. All patients were normotensive, in sinus rhythm and without evidence of heart failure, cardiomyopathy or valvular disease. Patients with a

history of glucose intolerance were excluded from the study. No patient had evidence of left ventricular hypertrophy or conduction defects that could interfere with the interpretation of ST segment changes, and no patient was taking digitalis. Calcium channel blocking and beta-adrenergic blocking agents were withdrawn 2 days before the study. Patients were also requested to abstain from xanthine-containing drugs and food and drink for at least 48 h before study. On completion of the diagnostic angiograms of both coronary arteries, the left coronary artery was recannulated with a 5F left Judkins catheter of appropriate size. Patients then underwent a randomized crossover study of the algogenic effects of the infusion of adenosine or the simultaneous infusion of substance P plus the same doses of adenosine into the left coronary artery (Fig. 1). Adenosine was infused at increasing scalar doses of 50, 100, 200, 400 and 800 μg/min for periods of 3 min each until the occurrence of pain. Substance P alone (11.2 pmol/min) was infused at the rate of 2 ml/min for 3 min, followed by the simultaneous infusion of substance P (11.2 pmol/min) plus the same doses of adenosine reported previously. At the onset of pain the infusion of adenosine or of substance P plus adenosine was continued to complete the infusion period of that particular dose of adenosine and was then stopped. Time to the onset of pain (in seconds from the beginning of the infusion) and maximal pain severity assessed by using a visual analog scale (16) were recorded. Four patients received adenosine; four patients received substance P plus adenosine as first infusion. Arterial blood pressure, obtained by way of the side port of the 7F femoral sheath, and the standard 12 ECG leads were continuously recorded throughout the study.

Assessment of pain. At the beginning of each adenosine or substance P plus adenosine infusion, patients were informed that they might experience pain or other unpleasant symptoms. This was not repeated during the infusion of adenosine or of substance P plus adenosine to avoid any potential bias. Patients were also instructed to report promptly the onset of pain and to record the maximal severity of the pain. Immediately after the test, while the patients were still in the catheterization laboratory, they were asked to report the maximal severity of pain using a visual analog scale (16). To this end the 100-mm scale was marked from no symptoms to severe symptoms. The scale was measured from zero to the subject's mark in millimeters. All subjects were unaware of the nature of the infused materials. Testing personnel were aware of the nature of the infused materials.

Statistical analysis. Statistical analysis of the hemodynamic data was performed using analysis of variance. The Student *t* test for paired data was used to compare the time to pain onset. Pain severity was analyzed with the Wilcoxon signed rank-sum test because this variable does not have a normal distribution. Visual analog scale data are expressed as median and range values. The remaining data are presented as mean value ± 1 SD. For purposes of this study, $p < 0.05$ was considered significant.

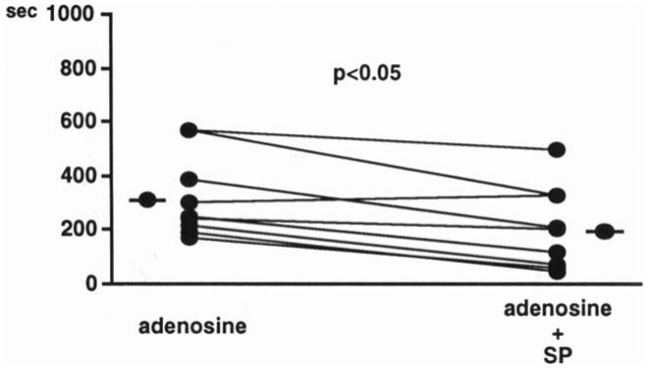


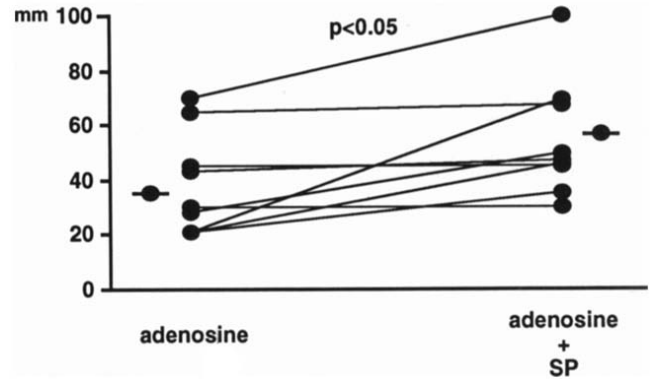
Figure 2. Effect of intrailiac artery infusion of adenosine alone and substance P (SP) plus adenosine on the time to onset of pain.

Results

Intrailiac infusion study. No patient experienced pain, discomfort or unpleasant symptoms during the infusion of substance P alone. Conversely, all patients experienced pain localized to the right leg during the infusion of both substance P plus adenosine and adenosine. Six patients described the pain as a feeling of heaviness localized at the right leg, and three patients experienced it as a cramp. In all patients time to onset of pain was shorter (207 ± 152 vs. 321 ± 154 s, $p < 0.05$) and pain severity was greater (47 mm [range 30–100] vs. 30 mm [range 21–70], $p < 0.05$) during simultaneous infusion of substance P plus adenosine than during adenosine infusion (Fig. 2 and 3). The type of pain during infusion of adenosine or substance P plus adenosine was similar. The pain disappeared spontaneously within 60 s of the end of infusion in all patients. Compared with baseline values, no patient exhibited ECG changes or changes in heart rate or mean arterial blood pressure during infusion of adenosine alone, substance P alone or substance P plus adenosine (73 ± 14 vs. 74 ± 13 vs. 72 ± 12 vs. 74 ± 13 beats/min, p = NS; 103 ± 10 vs. 103 ± 8 vs. 101 ± 10 vs. 100 ± 12 mm Hg, p = NS, respectively).

No patient experienced either pain or discomfort during infusion of the vehicle solution alone. All patients experienced pain localized to the right leg during infusion of both

Figure 3. Effect of the intrailiac artery infusion of adenosine alone and substance P (SP) plus adenosine on pain severity.



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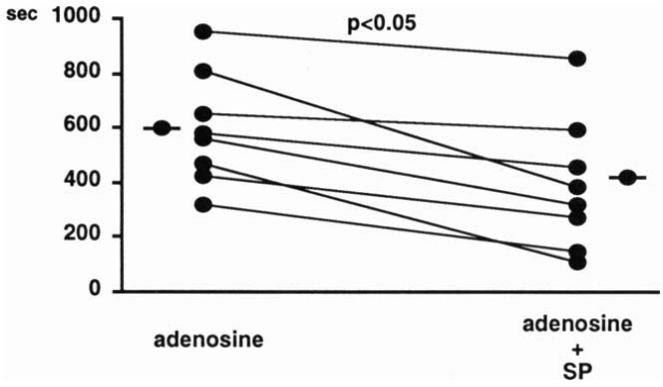

Figure 4. Effect of the intracoronary infusion of adenosine alone and substance P (SP) plus adenosine on the time to onset of pain.

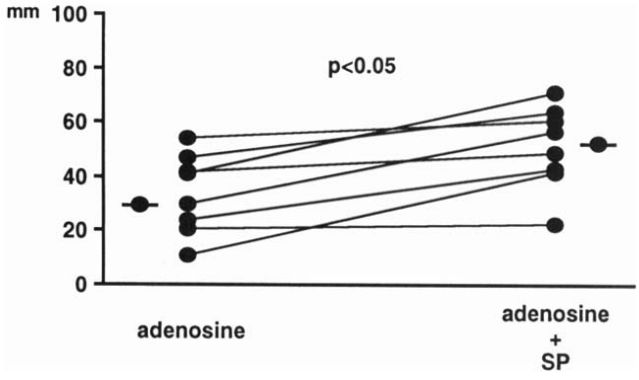

Figure 5. Effect of the intracoronary infusion of adenosine alone and substance P (SP) plus adenosine on pain severity.

substance P vehicle plus adenosine and adenosine alone. Five patients described the pain as a feeling of heaviness, and four patients experienced it as a cramp. In all patients time to onset of pain (331 ± 134 vs. 314 ± 155 s, p = NS) and pain severity (35 mm [range 20 to 71] vs. 30 mm [range 21 to 78], p = NS) were similar during both infusion of substance P vehicle plus adenosine and adenosine infusion. The type of pain during infusion of substance P vehicle plus adenosine or adenosine was similar. Pain disappeared spontaneously within 60 s of the end of infusion in all patients. Compared with baseline values, no patient exhibited ECG changes or changes in heart rate or mean arterial blood pressure during infusion of adenosine alone, substance P alone or substance P plus adenosine (72 ± 11 vs. 70 ± 9 vs. 70 ± 9 vs. 71 ± 7 beats/min, p = NS; 103 ± 10 vs. 102 ± 11 vs. 115 ± 11 vs. 103 ± 9 mm Hg, p = NS, respectively).

Intracoronary infusion study. No patient experienced pain during intracoronary infusion of substance P alone. All patients experienced pain similar to their usual anginal pain during the infusion of both substance P plus adenosine and adenosine. In all patients onset of pain occurred earlier (409 ± 242 vs. 596 ± 210 s, $p < 0.05$) and pain severity was greater (51 mm [range 21 to 69] vs. 33 mm [range 9 to 52], $p < 0.05$) during simultaneous infusion of substance P plus adenosine than during infusion of adenosine (Fig. 4 and 5). The type of pain during infusion of substance P plus adenosine or adenosine was similar. Pain disappeared within 60 s of the end of infusion in all patients. Compared with baseline values, no patient exhibited ECG changes or changes in heart rate or mean arterial blood pressure during infusion of adenosine alone, substance P alone or substance P plus adenosine (70 ± 16 vs. 71 ± 19 vs. 71 ± 16 vs. 69 ± 13 beats/min, p = NS; 99 ± 18 vs. 98 ± 16 vs. 100 ± 17 vs. 99 ± 16 mm Hg, p = NS, respectively).

Discussion

This study confirms that intraarterial infusion of substance P in humans does not cause pain (7–11). More important, our results show that substance P potentiates the algogenic effects of adenosine, thus suggesting that substance P causes muscular and cardiac hyperalgesia.

Role of substance P in modulation of peripheral algogenic stimuli. Since the discovery of substance P by von Euler and Gaddum in 1931 (17), considerable attention has been devoted to its involvement in the generation or transmission, or both, of nociceptive signals (4,18). Substance P has been implicated in the chemical activation of peripheral nociceptive neurons and in their sensitization, leading to primary hyperalgesia, that is, a localized lowering of the threshold to pain in an area of tissue damage (5,6,19–22). In the skin, substance P released from the peripheral nerve terminals, activated by tissue damage, induces several events leading to neurogenic inflammation (6). Indeed, substance P evokes changes in vascular caliber and permeability, releases a relaxant factor from vessel endothelium and stimulates the release of inflammatory mediators, such as interleukins, histamine, tissue necrosis factor and arachidonic acid (6,21,23–25), which, in turn, by stimulating the nerve terminals, may lead to further substance P release, thus causing a "positive feedback" circuit between the sensory neurons and the inflammatory cells (6). In this setting, the primary hyperalgesia caused by substance P might represent a protective mechanism by which subliminal stimuli can evoke pain.

Evidence of the involvement of substance P in the production of pain in humans is still circumstantial. In healthy volunteers and in patients with atopic dermatitis, the topical application of substance P evokes dose-dependent wheal, flare and itch reactions (23) that are partially due to histamine and cyclooxygenase products released from mast and other inflammatory cells (24,25). In patients with chronic pancreatitis, a significant intensification of the immunostaining for substance P was found in the peptidergic intralobular and interlobular nerves (26), suggesting that this peptide might be responsible for the long-lasting pain syndrome in chronic pancreatitis. Furthermore, substance P appears to facilitate pain perception by sensitizing peripheral nerve terminals to a variety of pain-producing agents. The injection of calcitonin gene-related peptide into the temporal muscle

of human volunteers does not induce more pain than placebo; however, when calcitonin gene-related peptide is injected in combination with substance P, a significantly more intense pain sensation is recorded (27). Similarly, the injection of bradykinin in the temporal muscle does not provoke more pain than saline solution, but the simultaneous injection of substance P and bradykinin significantly increases pain sensation and lowers the pressure pain threshold (28). Finally, whereas the cutaneous injection of neurokinin A does not produce pain, the simultaneous injection of substance P and neurokinin A provokes a painful sensation (29).

Interaction between adenosine and substance P in the genesis of muscular and cardiac pain. Adenosine, a major mediator of ischemic pain in humans (12–15), has been shown to stimulate cardiac afferent fibers in experimental models (30–32). Local ischemiclike pain can be provoked by adenosine injection into the brachial or iliac artery (13,33). Intracoronary administration of adenosine in patients with ischemic heart disease elicits angina pectoris-like pain, which is described as indistinguishable from their habitual anginal pain (14,15). In the present study intrailiac and intracoronary infusion of substance P facilitated adenosine-induced pain, suggesting an interaction between these two substances, perhaps at the level of muscular and cardiac nociceptors. The mechanism of this interaction cannot be deduced from the current study. One possibility is that it may result from a direct hyperalgesic effect of substance P on muscular and cardiac nociceptors. Alternatively, it might be due to substance P-mediated release of agents, such as protons, 5-hydroxytryptamine, bradykinin, histamine, prostaglandins and nitric oxide, which, in turn, would be directly responsible for the hyperalgesia (6,19–22). Finally, a central mechanism of hyperalgesia, such as sensitization of dorsal horn spinothalamic neurons (21) or an action at the level of substantia gelatinosa or thalamus, cannot be excluded. This seems unlikely, however, because no systemic hemodynamic effects were seen in our study during infusion of adenosine or substance P plus adenosine. It is also theoretically possible that the increased pain severity observed during simultaneous infusion of substance P plus adenosine might be attributable to an additional vasodilating effect of substance P, thus allowing wider distribution of adenosine. This possibility, however, is unlikely for the following reasons: First, substance P is a much less powerful vasodilator of the coronary resistance vessels than adenosine (7,8). Second, the simultaneous intraarterial infusion of adenosine and nifedipine, a potent vasodilator, does not potentiate the algogenic effects of adenosine (33). Finally, bamiphylline, a selective antagonist of A_1 adenosine receptors (34), prevents pain induced by intracoronary infusion of adenosine, but not the coronary vasodilator response (35), thus proving that the algogenic effects of adenosine are independent of its vasodilating action.

Study limitations. A critical issue in our study was the choice of an appropriate dose of substance P. The endothelium-dependent vasodilator effects of substance P have been extensively investigated in humans on capacitance and resistance peripheral vessels (7) and in the coronary circulation (8–11). The intracoronary infusion of 11.2 pmol/min of substance P was found to cause maximal coronary vasodilation within about 8 s in the absence of systemic hemodynamic effects (8). Therefore, in our study this dose was infused for 3 min before adenosine infusion, on the assumption that it was sufficient to produce maximal or near-maximal stimulation of muscular and cardiac sensory receptors. Another critical issue of our study was the assessment of pain. To this end we used the visual analog scale. This approach has been extensively validated by Huskisson (16). Its reliability is confirmed by the observation in this and in a previous study (35), that pain severity during infusion of adenosine before and after placebo is similar. Finally, in this study, testing personnel were not unaware of the nature of the infused materials. However, the greatest effort was made in following a very rigid protocol to avoid any potential bias. In particular, all patients were reminded that they could develop symptoms at the beginning of each infusion only, and this request was not repeated during the infusion. The patients themselves, who were unaware of the nature of the infused materials, marked the visual analog scale.

Conclusions and clinical implications. This study shows that the infusion of substance P causes muscular and cardiac hyperalgesia, which might be particularly important in the modulation of pain in the presence of tissue damage when substance P is likely to be released by nerve endings. Under these circumstances, substance P might amplify the well known algogenic effects of adenosine.

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